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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number:	WO 99/42104
A61K 31/435		(43) International Publication Date:	26 August 1999 (26.08.99)

(21) International Application Number: PCT/JP99/00681

(22) International Filing Date: 17 February 1999 (17.02.99)

(30) Priority Data:

PP 1955 23 February 1998 (23.02.98) AU
PP 2992 16 April 1998 (16.04.98) AU

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(81) Designated States: JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: USE OF MACROLIDE COMPOUNDS FOR TREATING GLAUCOMA

(57) Abstract

Macrolide compounds, such as the FK506 Substance and its related compounds, are provided for the prevention or treatment of eye diseases, particularly glaucoma. Composition containing such compounds is also disclosed.

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DESCRIPTION

USE OF MACROLIDE COMPOUNDS FOR TREATING GLAUCOMA

TECHNICAL FIELD

This invention relates to a new use of macrolide compounds for eye diseases. More specifically, this invention relates to a new use of macrolide compounds for preventing or treating glaucoma.

BACKGROUND ART

Glaucoma is a group of eye diseases characterized by an increase in intraocular pressure that causes pathological changes in the optic disk and typical defects in the field of vision. Normally, primary glaucoma (e.g., primary angle-closure glaucoma, primary open-angle glaucoma, etc.,), secondary glaucoma (e.g., secondary angle-closure glaucoma, secondary open-angle glaucoma, etc.,) and congenital glaucoma are exemplified as the particular ones thereof.

The progressive optic neuropathy that is accompanied by normal intraocular pressure, open iridocorneal angles and no evidence of other systemic disease is commonly termed normal-pressure glaucoma. 25% of patients suffering from glaucoma are regarded as the ones suffering normal-pressure glaucoma. Patients suffering from normal-pressure glaucoma also have neuronal damage, which results in loss of vision. However, the mechanism by which the damage occurs is not clearly understood.

Many macrolide compounds having immunosuppressive

activity are already known. For example, the tricyclic macrolide compound and its pharmaceutically acceptable salt for use in accordance with this invention is known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs.-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, etc.].

DISCLOSURE OF INVENTION

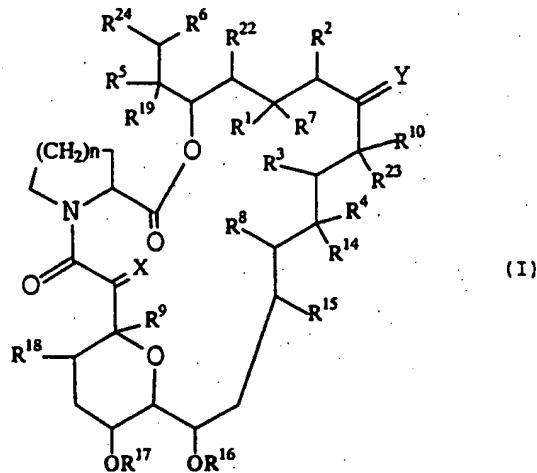
The inventors of this invention have surprisingly found that the macrolide compounds mentioned here-in-below are useful for preventing or treating eye diseases, such as, glaucoma, more particularly, normal-pressure glaucoma.

Accordingly, this invention provides a new use of the macrolide compounds for preventing or treating glaucoma.

Further, this invention provides a prophylactic or therapeutic agent for glaucoma, which comprises the macrolide compounds.

Still further, this invention provides a method for preventing or treating glaucoma, which comprises administering said macrolide compounds to mammals.

As a particular example of the macrolide compounds, the tricyclic compound of the following formula (I) can be exemplified.



(wherein each of adjacent pairs of R^1 and R^2 , R^3 and R^4 , and R^5 and R^6 independently

(a) is two adjacent hydrogen atoms, but R^2 may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R^7 is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R^1 ;

R^8 and R^9 are independently a hydrogen atom or a hydroxy group; R^{10} is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula $-CH_2O-$;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula N-NR¹¹R¹² or N-OR¹³; R¹¹ and R¹² are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group; R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ are independently a hydrogen atom or an alkyl group; R²⁴ is an optionally substituted ring system which may contain one or more heteroatoms; n is an integer of 1 or 2; and in addition to the above definitions, Y, R¹⁰ and R²³, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula -CH₂Se(C₆H₅), and an alkyl substituted by one or more hydroxy groups.

Preferable R²⁴ may be cyclo(C₅₋₇)alkyl group, and the following ones can be exemplified.

- (a) a 3,4-di-oxo-cyclohexyl group;
- (b) a 3-R²⁰-4-R²¹-cyclohexyl group,
in which R²⁰ is hydroxy, an alkoxy group, or a -OCH₂OCH₂CH₂OCH₃ group, and R²¹ is hydroxy, -OCN, an alkoxy group, a

heteroaryloxy which may be substituted by suitable substituents, a $-\text{OCH}_2\text{OCH}_2\text{CH}_2\text{OCH}_3$ group, a protected hydroxy group, chloro, bromo, iodo, aminoxyloxy, an azido group, p-tolyloxythiocarbonyloxy, or $\text{R}^{25}\text{R}^{26}\text{CHCOO}-$, in which R^{25} is optionally protected hydroxy or protected amino, and R^{26} is hydrogen or methyl, or R^{20} and R^{21} together form an oxygen atom in an epoxide ring; or

(c) cyclopentyl group substituted by methoxymethyl, optionally protected hydroxymethyl, acyloxymethyl (in which the acyl moiety optionally contains either a dimethylamino group which may be quaternized, or a carboxy group which may be esterified), one or more amino and/or hydroxy groups which may be protected, or aminoxyloxy. A preferred example is a 2-formyl-cyclopentyl group.

The definitions used in the above general formula (I) and the specific and preferred examples thereof are now explained and set forth in detail.

The term "lower" means, unless otherwise indicated, a group having 1 to 6 carbon atoms.

Preferable examples of the "alkyl groups" and an alkyl

moiety of the "alkoxy group" include a straight or branched chain aliphatic hydrocarbon residue, for example, a lower alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, neopentyl and hexyl.

Preferable examples of the "alkenyl groups" include a straight or branched chain aliphatic hydrocarbon residue having one double-bond, for example, a lower alkenyl group such as vinyl, propenyl (e.g., allyl group), butenyl, methylpropenyl, pentenyl and hexenyl.

Preferable examples of the "aryl groups" include phenyl, tolyl, xylyl, cumenyl, mesityl and naphthyl.

Preferable protective groups in the "protected hydroxy groups" and the "protected amino" are 1-(lower alkylthio)-(lower)alkyl group such as a lower alkylthiomethyl group (e.g., methylthiomethyl, ethylthiomethyl, propylthiomethyl, isopropylthiomethyl, butylthiomethyl, isobutylthiomethyl, hexylthiomethyl, etc.), more preferably C₁-C₄ alkylthiomethyl group, most preferably methylthiomethyl group;

trisubstituted silyl group such as a tri(lower)alkylsilyl (e.g., trimethylsilyl, triethylsilyl, tributylsilyl, tert-butyldimethylsilyl, tri-tert-butylsilyl, etc.) or lower alkyl-diarylsilyl (e.g., methyldiphenylsilyl, ethyldiphenylsilyl, propyldiphenylsilyl, tert-butyldiphenylsilyl, etc.), more preferably tri(C₁-C₄)alkylsilyl group and C₁-C₄ alkyldiphenylsilyl group, most preferably tert-butyldimethylsilyl group and tert-butyldiphenylsilyl group;

and an acyl group such as an aliphatic, aromatic acyl group or an aliphatic acyl group substituted by an aromatic group, which are derived from a carboxylic acid, sulfonic acid or carbamic acid.

Examples of the aliphatic acyl groups include a lower alkanoyl group optionally having one or more suitable substituents such as carboxy, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, hexanoyl, carboxyacetyl, carboxypropionyl, carboxybutyryl, carboxyhexanoyl, etc.; a cyclo(lower)alkoxy(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkyl, e.g., cyclopropyloxyacetyl, cyclobutyloxypropionyl, cycloheptyloxybutyryl, menthyloxyacetyl, menthyloxypropionyl, menthyloxybutyryl, menthyloxpentanoyl, menthyloxyhexanoyl, etc.; a camphorsulfonyl group; or a lower alkylcarbamoyl group having one or more suitable substituents such as carboxy or protected carboxy, for example, carboxy(lower)alkylcarbamoyl group (e.g., carboxymethylcarbamoyl, carboxyethylcarbamoyl, carboxypropylcarbamoyl, carboxybutylcarbamoyl, carboxypentylcarbamoyl, carboxyhexylcarbamoyl, etc.), tri-(lower)alkylsilyl(lower)alkoxycarbonyl(lower)alkylcarbamoyl group (e.g., trimethylsilylmethoxycarbonylethylcarbamoyl, trimethylsilylethoxycarbonylpropylcarbamoyl, triethylsilylethoxycarbonylpropylcarbamoyl, tert-butyldimethylsilylethoxycarbonylpropylcarbamoyl, tri-

methylsilylpropoxycarbonylbutylcarbamoyl, etc.) and so on.

Examples of the aromatic acyl groups include an aroyl group optionally having one or more suitable substituents such as nitro, e.g., benzoyl, toluoyl, xyloyl, naphthoyl, nitrobenzoyl, dinitrobenzoyl, nitronaphthoyl, etc.; and an arenesulfonyl group optionally having one or more suitable substituents such as halogen, e.g., benzenesulfonyl, toluenesulfonyl, xylenesulfonyl, naphthalenesulfonyl, fluorobenzenesulfonyl, chlorobenzenesulfonyl, bromobenzenesulfonyl, iodobenzenesulfonyl, etc.

Examples of the aliphatic acyl groups substituted by an aromatic group include ar(lower)alkanoyl group optionally having one or more suitable substituents such as lower alkoxy or trihalo(lower)alkyl, e.g., phenylacetyl, phenylpropionyl, phenylbutyryl, 2-trifluoromethyl-2-methoxy-2-phenylacetyl, 2-ethyl-2-trifluoromethyl-2-phenylacetyl, 2-trifluoromethyl-2-propoxy-2-phenylacetyl, etc.

More preferable acyl groups among the aforesaid acyl groups are C₁-C₄ alkanoyl group optionally having carboxy, cyclo(C₅-C₆) alkoxy(C₁-C₄) alkanoyl group having two (C₁-C₄) alkyls at the cycloalkyl moiety, camphorsulfonyl group, carboxy-(C₁-C₄) alkylcarbamoyl group, tri(C₁-C₄) alkylsilyl(C₁-C₄)-alkoxycarbonyl(C₁-C₄) alkylcarbamoyl group, benzoyl group optionally having one or two nitro groups, benzenesulfonyl group having halogen, or phenyl(C₁-C₄) alkanoyl group having C₁-C₄ alkoxy and trihalo(C₁-C₄) alkyl group. Among these, the most

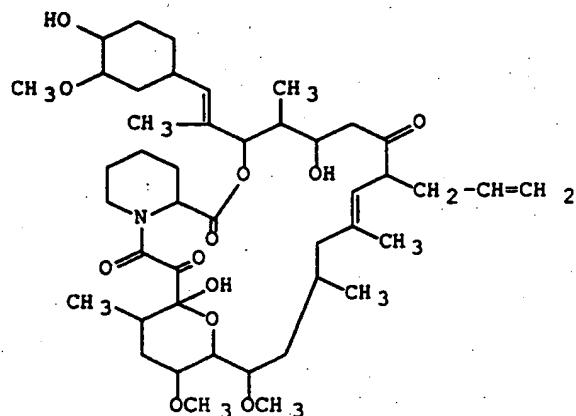
preferable ones are acetyl, carboxypropionyl, menthyloxyacetyl, camphorsulfonyl, benzoyl, nitrobenzoyl, dinitrobenzoyl, iodobenzenesulfonyl and 2-trifluoromethyl-2-methoxy-2-phenylacetyl.

Preferable examples of the "5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring" include a pyrrolyl group and a tetrahydrofuryl group.

The tricyclic compounds (I) and its pharmaceutically acceptable salt for use in accordance with this invention are well known to have excellent immunosuppressive activity, antimicrobial activity and other pharmacological activities and, as such, be of value for the treatment or prevention of rejection reactions by transplantation of organs or tissues, graft-vs-host diseases, autoimmune diseases, and infectious diseases [EP-A-0184162, EP-A-0323042, EP-A-423714, EP-A-427680, EP-A-465426, EP-A-480623, EP-A-532088, EP-A-532089, EP-A-569337, EP-A-626385, WO89/05303, WO93/05058, WO96/31514, WO91/13889, WO91/19495, WO93/5059, etc.] , the disclosures of which are incorporated herein by reference.

Particularly, the compounds which are designated as FR900506 (=FK506), FR900520 (ascomycin), FR900523, and FR900525 are products produced by microorganisms of the genus Streptomyces, such as Streptomyces tsukubaensis No. 9993 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly

Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit October 5, 1984, accession number FERM BP-927] or Streptomyces hygroscopicus subsp. yakushimaensis No. 7238 [deposited with National Institute of Bioscience and Human Technology Agency of Industrial Science and Technology (formerly Fermentation Research Institute Agency of Industrial Science and Technology), at 1-3, Higashi 1-chome, Tsukuba-shi, Ibaraki, Japan, date of deposit January 12, 1985, accession number FERM BP-928] [EP-A-0184162]. The FK506 Substance (general name: tacrolimus) of the following chemical formula, in particular, is a representative compound.



Chemical name: 17-allyl-1,14-dihydroxy-12-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylvinyl]-23,25-dimethoxy-13,19,21,27-tetramethyl-11,28-dioxa-4-azatricyclo[22.3.1.0^{4,9}]octacos-18-ene-2,3,10,16-tetraone

The preferred examples of the tricyclic compounds (I) are the ones, wherein each of adjacent pairs of R³ and R⁴ or R⁵ and R⁶ independently form another bond formed between the carbon atoms to which they are attached;

each of R⁸ and R²³ is independently a hydrogen atom;

R⁹ is a hydroxy group;

R¹⁰ is a methyl group, an ethyl group, a propyl group or an allyl group;

X is (a hydrogen atom and a hydrogen atom) or an oxo group;

Y is an oxo group;

each of R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, and R²² is a methyl group;

R²⁴ is a 3-R²⁰-4-R²¹-cyclohexyl group,

in which R²⁰ is hydroxy, an alkoxy group, or a -OCH₂OCH₂CH₂OCH₃ group, and

R²¹ is hydroxy, -OCN, an alkoxy group, a heteroaryloxy which may be substituted by suitable substituents, a -OCH₂OCH₂CH₂OCH₃ group, a protected hydroxy group, chloro, bromo, iodo, aminoxyloxy, an azido group, p-tolyloxythiocarbonyloxy, or R²⁵R²⁶CHCOO-,

in which R²⁵ is optionally protected hydroxy or protected amino, and

R²⁶ is hydrogen or methyl, or

R²⁰ and R²¹ together form an oxygen atom in an epoxide ring; and

n is an integer of 1 or 2.

The most preferable tricyclic compounds (I) is, in addition to FK506, ascomycin derivatives such as halogenated-ascomycin (e.g., 33-epi-chloro-33-desoxyascomycin), which is disclosed in EP 427,680, example 66a.

As the other preferable example of the macrolide as immunosuppressants, rapamycin [THE MERCK INDEX (12th edition), No. 8288] and its derivatives can be exemplified. Preferred example of the derivatives is an O-substituted derivative in which the hydroxy in position 40 of formula A illustrated at page 1 of WO 95/16691, incorporated herein by reference, is replaced by -OR₁ in which R₁ is hydroxyalkyl, hydroalkoxyalkyl, acylaminoalkyl and aminoalkyl; for example 40-O-(2-hydroxy)ethyl-rapamycin, 40-O-(3-hydroxy)propyl-rapamycin, 40-O-[2-(2-hydroxy)ethoxy]ethyl-rapamycin and 40-O-(2-acetaminoethyl)-rapamycin. These O-substituted derivatives may be produced by reacting rapamycin (or dihydro or deoxo-rapamycin) with an organic radical attached to a leaving group (for example RX where R is the organic radical which is desired as the O-substituent, such as an alkyl, allyl, or benzyl moiety, and X is a leaving group such as CCl₃C(NH)₂O or CF₃SO₃) under suitable reaction conditions. The conditions may be acidic or neutral conditions, for example in the presence of an acid like trifluoromethanesulfonic acid, camphorsulfonic acid, p-

toluenesulfonic acid or their respective pyridinium or substituted pyridinium salts when X is $\text{CCl}_3\text{C}(\text{NH})\text{O}$ or in the presence of a base like pyridine, a substituted pyridine, diisopropylethylamine or pentamethylpiperidine when X is CF_3SO_3^- . The most preferable one is 40-O-(2-hydroxy)ethyl rapamycin, which is disclosed in WO94/09010, the disclosure of which is incorporated herein by reference.

The tricyclic compounds(I), and rapamycin and its derivatives, have a similar basic structure, i.e., tricyclic macrolide structure, and at least one of the similar biological properties (for example, immunosuppressive activity).

The tricyclic compounds(I), and rapamycin and its derivatives, may be in a form of its salt, which includes conventional non-toxic and pharmaceutically acceptable salt such as the salt with inorganic or organic bases, specifically, an alkali metal salt such as sodium salt and potassium salt, an alkali earth metal salt such as calcium salt and magnesium salt, an ammonium salt and an amine salt such as triethylamine salt and N-benzyl-N-methylamine salt.

With respect to the macrolide compounds usable in the present invention, it is to be understood that there may be conformers and one or more stereoisomers such as optical and geometrical isomers due to asymmetric carbon atom(s) or double

bond(s), and such conformers and isomers are also included within the scope of the present invention. And further, the macrolide compounds can be in the form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

The macrolide compounds usable in the present invention may be administered as pure compounds or mixtures of compounds or preferably, in a pharmaceutical vehicle or carrier.

The pharmaceutical compositions of this invention can be used in the form of a pharmaceutical preparation, for example, in solid, semisolid or liquid form, which contains the macrolide compounds of the present invention, as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, or parenteral applications. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable, carriers for tablets, pellets, capsules, eye drops, suppositories, solutions (saline, for example), emulsion, suspensions (olive oil, for example), ointment and any other form suitable for use. The carriers which can be used are water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, corn starch, keratin, colloidal silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary,

stabilizing, thickening and coloring agents and perfumes may be used. The active object compound is included in the pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the disease.

Mammals which may be treated using the method of the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans.

For applying this composition to a human, it is preferable to apply it by external (topical) administration, particularly in the form of eye drops.

While the dosage of therapeutically effective amount of the macrolide compounds varies from and also depends upon the age and condition of each individual patient to be treated, a daily dose of about 0.0001-1000 mg, preferably 0.001-500 mg and more preferably 0.01-100 mg. of the active ingredient is generally given for treating diseases, and an average single dose of about 0.001-0.01mg, 0.2-0.5 mg, 1 mg, 5 mg, 10 mg, 50 mg, 100 mg, 250 mg and 500 mg is generally administered. Daily doses for chronic administration in humans will be in the range of about 0.1-0.3 mg/kg/day.

The most suitable disease among glaucoma is normal-pressure glaucoma. Normal-pressure glaucoma patients have been found to have increased serum immunoreactivity to human Heat Shock Proteins (Hsp), particularly Hsp60. Therefore, Glaucomatous optic neuropathy in a cohort of patients with

normal-pressure glaucoma deems to involve aberrant autoimmunity (Am. J. Ophthalmol., 1998; 125 145-157), the disclosure of which is incorporated herein by reference.

The effectiveness of the macrolide compounds on normal-pressure glaucoma can be confirmed by evaluating the inhibiting activity on such aberrant autoimmunity, as well as the direct treatment of patients suffering from normal-pressure glaucoma. Particularly, the eye drop prepared in the below mentioned Example 2, which contains FK506 Substance, can inhibit the aberrant autoimmunity and is quite effective for treating glaucoma, particularly normal-pressure glaucoma.

The following examples are given for the purpose of illustrating the present invention.

Example 1

FK 506 Substance	1 g
Hydroxypropyl methylcellulose 2910 (TC-5R)	1 g
Lactose	2 g
Croscarmellose sodium (Ac-Di-Sol)	1 g

The FK 506 Substance (1 g) was dissolved in ethanol (10 ml), and thereto was added hydroxypropyl methylcellulose 2910 (TC-5R) (1 g) to prepare a suspension. To this suspension was added dichloromethane (5 ml) to prepare a homogeneous solution. Lactose (2 g) and croscarmellose sodium (Trade Mark: Ac-Di-

Sol, maker: Asahi Chemical Industry) were homogeneously suspended to this solution, and then the organic solvent was removed by evaporation. The residual product was dried under reduced pressure for 10 hours by vacuum dryer, milled for 2 minutes by coffee mill and then passed through a sieve (32 mesh) to give the solid dispersion composition of FK 506 Substance (5 g). This composition was capsulated by a conventional manner to provide capsules containing 1 mg or 5 mg of FK 506 Substance per each capsule.

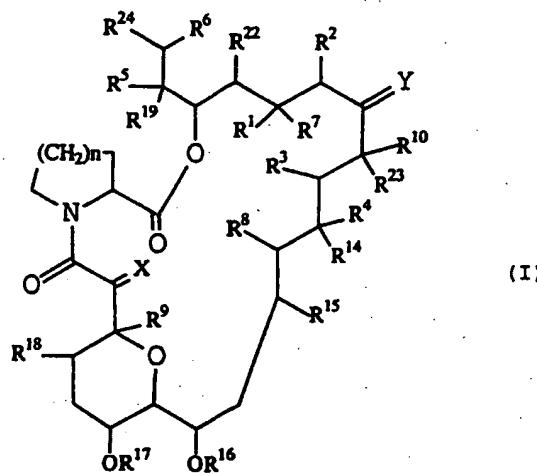
Example 2

FK 506 Substance (fine powder)	1 mg
Polysorbate 80	0.5mg
Polyvinyl alcohol	2.8mg
Benzalkonium chloride	0.1mg
Sodium chloride	8.6mg
pH5.25 Phosphate buffer	to 1 ml

An aqueous suspending eye drop containing the above-mentioned ingredients is prepared according to a conventional manner shown in EP-A-0406791, the disclosure of which is incorporated herein by reference.

CLAIMS

1. A use of macrolide compounds for manufacturing a medicament for preventing or treating glaucoma.
2. The use of Claim 1, in which the macrolide compounds is the tricyclic compounds of the following formula (I) :



(wherein each of adjacent pairs of R¹ and R², R³ and R⁴, and R⁵ and R⁶ independently

(a) is two adjacent hydrogen atoms, but R² may also be an alkyl group or

(b) may form another bond formed between the carbon atoms to which they are attached;

R⁷ is a hydrogen atom, a hydroxy group, a protected hydroxy group, or an alkoxy group, or an oxo group together with R¹;

R⁸ and R⁹ are independently a hydrogen atom or a hydroxy group;

R¹⁰ is a hydrogen atom, an alkyl group, an alkyl group substituted by one or more hydroxy groups, an alkenyl group, an alkenyl

group substituted by one or more hydroxy groups, or an alkyl group substituted by an oxo group;

X is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula -CH₂O-;

Y is an oxo group, (a hydrogen atom and a hydroxy group), (a hydrogen atom and a hydrogen atom), or a group represented by the formula N-NR¹¹R¹² or N-OR¹³;

R¹¹ and R¹² are independently a hydrogen atom, an alkyl group, an aryl group or a tosyl group;

R¹³, R¹⁴, R¹⁵, R¹⁶, R¹⁷, R¹⁸, R¹⁹, R²² and R²³ are independently a hydrogen atom or an alkyl group;

R²⁴ is an optionally substituted ring system which may contain one or more heteroatoms;

n is an integer of 1 or 2; and

in addition to the above definitions, Y, R¹⁰ and R²³, together with the carbon atoms to which they are attached, may represent a saturated or unsaturated 5- or 6-membered nitrogen, sulfur and/or oxygen containing heterocyclic ring optionally substituted by one or more groups selected from the group consisting of an alkyl, a hydroxy, an alkoxy, a benzyl, a group of the formula -CH₂Se(C₆H₅), and an alkyl substituted by one or more hydroxy groups.

3. A method for preventing or treating glaucoma, which comprises administering macrolide compounds to mammals.

4. A pharmaceutical composition for treating or preventing glaucoma, which comprises macrolide compounds in admixture with a carrier or excipient.

5. A process for preparing the pharmaceutical composition of Claim 4, which is characterized by admixing the macrolide compounds with a carrier or excipient.

6. The macrolide compound used in Claims 1 to 5 is FK 506 Substance.

7. The glaucoma in Claims 1 is normal-pressure glaucoma.

INTERNATIONAL SEARCH REPORT

International application No
PCT/JP 99/00681

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/435

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 98 41205 A (CHILDRENS MEDICAL CENTER) 24 September 1998 see abstract see page 18 - page 24 see page 17, line 7 - line 14 see page 31, line 17 - line 20; claims 1-8 --- 	1,3-5
X	WO 94 13275 A (MASSACHUSETTS EYE AND EAR INFI ;CHILDRENS MEDICAL CENTER (US)) 23 June 1994 see the whole document, in particular page 13, last compound mentioned --- 	1-7
X	EP 0 532 862 A (UNIV LOUISVILLE RES FOUND) 24 March 1993 see abstract see page 2, column 1, line 45 - line 51; claims --- -/-/	1,3-5,7

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "O" document referring to an oral disclosure, use, exhibition or other means
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

29 June 1999

Date of mailing of the international search report

12/07/1999

Name and mailing address of the ISA

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Authorized officer

Hoff, P

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 99/00681

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	G.C.Y. CHIOU: "Recent advances in antiglaucoma drugs" BIOCHEMICAL PHARMACOLOGY, vol. 30, 1981, pages 103-106, XP002107525 see page 105, left-hand column, paragraph 2 - right-hand column, paragraph 1 ---	1,3-5,7
X	WO 97 31020 A (GEN HOSPITAL CORP) 28 August 1997 see abstract see page 17, line 24 - page 19, line 11 see page 28, line 14 - line 25; claims ---	4-6
A	WO 92 19278 A (KURUME UNIVERSITY) 12 November 1992 see the whole document ---	1-3,7
X	EP 0 484 936 A (FUJISAWA PHARMACEUTICAL CO) 13 May 1992 see the whole document ---	4-6
X	EP 0 184 162 A (FUJISAWA PHARMACEUTICAL CO) 11 June 1986 cited in the application see abstract see page 66, line 33 - page 67, line 6; claims 1,15-18; examples ---	4-6
X	PLEYER U ET AL: "Ocular absorption of topically applied FK506 from liposomal and oil formulations in the rabbit eye 'published erratum appears in Invest Ophthalmol Vis Sci 1993 Nov;34(12):3481!.' INVESTIGATIVE OPHTHALMOLOGY AND VISUAL SCIENCE, (1993 AUG) 34 (9) 2737-42. JOURNAL CODE: GWI. ISSN: 0146-0404., XP002107526 United States see the whole document ---	4-6
A	SALAS-PRATO M ET AL: "Inhibition by rapamycin of PDGF- and bFGF-induced human tenon fibroblast proliferation in vitro." JOURNAL OF GLAUCOMA, (1996 FEB) 5 (1) 54-9. JOURNAL CODE: CMA. ISSN: 1057-0829., XP002107527 United States see the whole document ---	1-3,7
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 99/00681

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 3 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds which are theoretically contained within the definition "macrolide" of claim 1 the search had to be restricted on economic grounds. The search was limited to the general idea of the invention and to the compounds mentioned in claim 2 (Art. 6 PCT, Guidelines Chapt.II.7, last sentence and Chapt.III,3.7).

Claims searched completely:

2,6

Claims searched incompletely: 1,3,4,5,7

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